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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HEINRICH RÖDER, MAXIM TSYPIN, and JULIA GRIGORIEVA

Appeal 2016-000289
Application 12/806,137[1]
Technology Center 1700

Before KAREN M. HASTINGS, GEORGE C. BEST, and WESLEY B. DERRICK, *Administrative Patent Judges*.

DERRICK, *Administrative Patent Judge*.

DECISION ON APPEAL

STATEMENT OF THE CASE

Appellants appeal under 35 U.S.C. § 134 from the Examiner's maintained 35 U.S.C. § 103(a) rejections of claims 1–11. We have jurisdiction under 35 U.S.C. § 6.

We AFFIRM-IN-PART.

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[1] Appellants identify the real party in interest as Biodesix, Inc. Appeal Brief filed May 24, 2014 ("Appeal Br."), 2.

THE INVENTION

The subject matter of the claims on appeal relates to a system for determining whether a drug will be effective on a patient with a disease. Spec. Title; Claim 1.

Claim 1—the sole independent claim on appeal—is representative.

1. A laboratory test processing center, comprising:

one or more data storage devices storing (a) class-labeled matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF)-derived mass spectral data obtained from blood-based samples of a multitude of cancer patients, the class labels for the mass spectral data indicating whether or not a patient associated with the mass spectral data was responsive to treatment of cancer from administration of a cancer targeting drug; and (b) a multitude of MALDI-TOF-derived mass spectra of blood-based samples of a multitude of cancer patients to be tested;

a processing unit operating in accordance with a set of instructions to perform the following operations on the multitude of mass spectra of the blood-based samples of a multitude of cancer patients to be tested and the class-labeled mass spectral data:

(a) perform one or more predefined pre-processing steps on the multitude of MALDI-TOF-derived mass spectra of the blood-based samples of a multitude of cancer patients to be tested;

(b) obtain integrated intensity values of features in the mass spectra of the blood-based samples of the multitude of cancer patients to be tested at one or more predetermined m/z ranges in said mass spectra after the performance of said predefined pre-processing steps;

c) implement a classification algorithm on the integrated intensity values and the class-labeled mass spectral data, the classification algorithm assigning a class label for each of the multitude of mass spectra; and

d) output the class label assigned by the classification algorithm to each of the multitude of mass spectra of the cancer patients to be tested.

Appeal Br. (Claims Appendix) 17.

THE REJECTIONS[2]

The claims stand rejected under 35 U.S.C. § 103 as follows:

I. Claims 1, 2, 4–6, 10, and 11 over Xiao;[3]

II. Claim 7 over Xiao in view of Zhao;[4]

III. Claim 8 over Xiao in view of Zhao and Mazet;[5] and

IV. Claims 3 and 9 over Xiao in view of Lynch.[6]

DISCUSSION

We have reviewed Appellant's arguments for patentability set forth in the Appeal Brief and the Reply Brief filed September 30, 2015 ("Reply Br.") but, as explained below, are not persuaded that the Examiner erred reversibly in rejecting the claims except as to claim 6 (subject to Rejection I.

Accordingly, we affirm the rejections of claims 1, 2, 4, 5, 7, 8, 10, and 11, and we reverse the rejections of claim 6.

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[2] We refer to the Final Office Action mailed October 23, 2014 ("Final Act.") and the Examiner's Answer mailed July 30, 2015 ("Ans.").
[3] Xiao et al., *Serum Proteomic Profiles Suggest Celeocoxib-Modulated Targets and Response Predictors*, 64 Cancer Res. 2904–2909 (2004).
[4] Zhao et al., US 2005/0048547 A1, published March 3, 2005.
[5] Mazet et al., *Background Removal from Spectra by Designing and Minimising a Non-Quadratic Cost Function*, 76 Chemometrics & Intelligent Lab. Sys. 121–33 (2005).
[6] Lynch et al., *Activating Mutations in the Epidermal Growth Factor Receptor Underlying responsiveness of Non-Small-Cell Lung Cancer to Gefitinib*, 350 New Eng. J. Med. 2129–39 (2004).

Rejection I

Xiao describes aspects of a cancer prevention trial using celecoxib in familial adenomatous polyposis (FAP) patients. The Examiner relies on Xiao for its disclosure of a laboratory test processing center comprising: (1) data storage devices for storing; (a) class-labeled matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF)-derived mass spectra data from blood-based samples of pre-cancer patients and (b) a mass spectrum of a blood-based sample of a pre-cancer patient to be tested; and (2) a processing unit operating in accordance with instructions to (a) perform one or more pre-processing steps, (b) obtain integrated intensity values of features in the patient sample mass spectrum, (c) implement a classification algorithm to provide an indication of whether the patient is likely to benefit from administration of a cancer targeting drug, and (d) output the class label (responder or non-responder) assigned by the classification algorithm to the sample as set forth in claim 1. Ans. 2–3.

As to the laboratory test processing center's use to store and analyze cancer patient data, the Examiner also relies on Xiao's disclosure. The "pre-cancer patient" and related group of patients for testing as drug responder or non-responder are individuals with FAP, which—as emphasized by the Examiner—"have a marked predisposition to colorectal carcinoma and develop numerous adenomatous polyps, considered to be premalignant precursors to carcinoma." Ans. 3 (citing Xiao 2904, ¶ 1). Celecoxib, the particular drug for which response was tested in Xiao, targets cyclooxygenase 2 (COX-2), which—as emphasized by the Examiner—Xiao teaches is a valid target for cancer prevention and treatment." Ans. 3 (citing Xiao, Abstract).

The Examiner then concludes in essence that it would have been obvious at the time of the invention to use Xiao's method for analysis of colorectal cancer patients because of the related nature of FAP and colorectal cancer and the action of the drug targeting COX-2 in the treatment of both FAP and the related cancer. Ans. 3.

Further, the Examiner reasonably finds the disclosed structure of Xiao's apparatus meets the limitations of claim 1 because it is capable of performing the intended use relating to cancer patients. Ans. 3–4. The Examiner's determination that Xiao meets the claim includes that:

> The data storage device of Xiao's test data processing center is capable of storing (a) class-labeled matrix-assisted laser desorption/ionization (MALOI) time-of-flight (TOF)-derived mass spectral data obtained from blood-based samples of a multitude of cancer patients. The processing unit of Xiao is capable of operating in accordance with a set of instructions to perform the following operations on the multitude of mass spectra of the blood-based samples of a multitude of cancer patients to be tested and the class-labeled mass spectral data.

Ans. 4, see also 10–11.

Appellants proffer arguments as to the claims subject to Rejection I as a group—which we discuss in regard to independent claim 1—as well as additional arguments as to dependent claims 4, 6, 10, and 11.

Appellants contend that there is no basis for one of skill in the art to have understood that "class labels generated by the laboratory test processing centers could be used to indicate whether or not the cancer patients will likely be responsive to treatment of cancer by administration of a cancer targeting drug." Appeal Br. 4. Appellants argue that Xiao's identification of a marker for FAP patients "in no way teaches or suggests" markers could be developed for cancer patients and that the Examiner is

improperly relying on an "obvious to try rationale" for which the requisite reasonable expectation of success is lacking. Appeal Br. 4–6. The arguments are grounded on FAP and colorectal cancer being different diseases and on the unpredictability of response to cancer treatments. Appeal Br. 4–5; see also Reply Br. 1–2.

On this record, we are not persuaded of reversible error in the Examiner's reliance on Xiao. While Appellants argue that FAP and colorectal cancer are different, they fail to squarely address the Examiner's reasoning grounded on the related nature of the two diseases, including that the drug tested in Xiao—celecoxib—targets COX-2, a known target—for "cancer prevention and treatment." *Cf. In re Preda*, 401 F.2d 825, 826 (CCPA 1968) ("[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference, but also the inference which one skilled in the art would reasonably be expected to drawn therefrom."). Moreover, the "prior art reference must be 'considered together with the knowledge of one of ordinary skill in the pertinent art.'" *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (quoting *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). In this case, the reasonable inferences to be drawn from Xiao include that markers indicating responsiveness to celecoxib would be present in both pre-cancer, FAP patients and colorectal cancer patients as COX-2 is the target in the treatment of both conditions. *See, e.g.*, Xiao Abstract. As to the unpredictability of response to cancer treatments, the issue is not that a particular cancer treatment may or may not work, but rather that there is a correlation between a marker and treatment efficacy, and Appellants' arguments fail to address this with any cogent argument. *See generally* Appeal Br.; Reply Br.

Appellants also contend that there is a structural difference between the laboratory test processing center of the instant claims and that disclosed in Xiao on the basis that claims requiring data from cancer patients rather than from FAP patients without cancer. Appeal Br. 6–7. In response to the cancer patient limitation being merely an intended use, Appellants argue that the recited storage devices are not capable of performing the intended use because Xiao does not include data from cancer patients.[7] Reply Br. 3–4.

On this record, we are not persuaded that the Examiner erred reversibly because the requirement that the data be from cancer patients does not further limit the structure of the claimed apparatus in a manner that patentably distinguishes it from Xiao's apparatus. The patentability of an apparatus "depends on the claimed structure, not on the use or purpose of that structure." *Catalina Mktg. Int'l. Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Appellants' argument is in essence that the data differs, but this fails to apprise us of any difference in the structure, including in necessary programming, required for Xiao's apparatus to perform the intended function of the claimed apparatus. *Cf. Typhoon Touch Techs., Inc. v. Dell, Inc.*, 659 F.3d 1376, 1380 (Fed. Cir. 2011) ("[T]he apparatus as provided must be 'capable' of performing the recited function, not that it might be modified to perform the function.").

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[7] Appellants further argument as to claim 2 that its recitation that "'production and storage of the mass spectrum in the one or data storage devices' . . . is a structural element" (Reply Br. 4) is not timely as the Examiner found Xiao's device meeting the limitation in being "capable of storing data relating to a cancer patient treated by a cancer targeting drug (Final Act. 4) and, in the absence of an explanation why Appellants could not have addressed it in the Appeal Brief, we deem the argument waived (37 C.F.R. § 41.41(b)(2)).

Claim 4

Claim 4 further recites that "one or more of the predetermined m/z ranges are selected from" a listing of particular ranges. Claim 4.

The Examiner finds, *inter alia*, that the limitation to the predetermined m/z ranges "merely describes the intended use of the processing unit and does not further limit the structure of the processing unit." Ans. 5. The Examiner further finds Xiao's processing unit is capable of processing data with the predetermined m/z ranges selected from the group recited in claim 4. Ans. 5; see also Xiao Tables 1–3.

Appellants contend the Examiner is relying on an obvious to try rationale and argue that that there is no proper basis for the recited m/z ranges, particularly where there is no teaching that different cancers have different m/z ranges and Xiao does not disclose a marker within a claimed range or for cancer. Appeal Br. 7–9; Reply Br. 5–6.

Appellants' arguments are not persuasive of reversible error because they fail to address the Examiner's rationale for the rejection of claim 4 grounded on the recited predetermined m/z ranges not constituting a structural limitation that distinguishes the claimed apparatus from Xiao's apparatus which relates to processing data that includes similar m/z values.

Claim 6

Appellants contend that the Examiner's "assert[ion] that a '[p]robabilistic k-nearest neighbor classification algorithm with improved performance is well-known in the art'" is an improper use of judicial or administrative notice. Appeal Br. 9–10.

On this record, the Examiner's assertion of fact (Final Act. 5), which is not later supported by citation to evidence (*see generally* Ans.), is

improper for the reasons highlighted by Appellants' argument, including that it relates to an area of specific knowledge of the prior art. Accordingly, we are unable to sustain the rejection of claim 6.

Claims 10 & 11

Citing the Examiner's statements regarding what Xiao teaches that include reference to "cancer patients" (Appeal Br. 10; Final Act. 5), Appellants contend the Examiner erred in the rejection of both claims 10 and 11 because "Xiao teaches absolutely nothing about cancer patients and therefore cannot support an obviousness rejection" (Appeal Br. 10).

Appellants' argument is not persuasive of harmful error because, as explained above, Xiao's explicit teaching as to pre-cancer, FAP reasonably teaches the skilled artisan the like methods for analysis of cancer patients. *In re Fritch*, 972 F.2d 1260, 1264–65 (Fed. Cir. 1992); *Preda*, 401 F.2d at 826. Appellants' argument here, accordingly, establishes no error in the Examiner's determination that one of ordinary skill in the art, armed with knowledge of Xiao, at the time of the invention, would have been led to the subject matter of claims 10 and 11.

Rejection II

In rejecting claim 7, the Examiner further relies on Xiao for its disclosure of predefined pre-processing steps, including subtracting background contained in the mass spectrum of the blood-based sample of the patient to produce a background subtracted spectrum, normalizing the background subtracted spectrum, and aligning the normalized, background subtracted spectrum to a predefined mass scale. Ans. 6 (citing Xiao 2905, ¶ 3).

The Examiner relies on Zhao for its teaching that the subtracting step comprises estimating non-constant levels of background and subtracting the estimated background from the mass spectral data, particularly with the use of a moving window (sliding window) using locally weighted background levels in the calculations. Ans. 6 (citing Zhao ¶¶ 50, 73).

The Examiner concludes that one of ordinary skill in the art, armed with the teachings of Xiao and Zhao, at the time of the invention, would have found it obvious to estimate non-constant levels of background and subtracting the estimated background from the mass spectral data for the benefit of more accurately estimating the background. Ans. 6; *see also* Ans. 11–12.

Appellants argue that Zhao does not correct the deficiencies of Xiao, but do not otherwise address the relied on teachings of Xiao. Appeal Br. 10–12. Appellants' arguments as to Zhao are directed wholly to portions other than ¶¶ 53 & 70 and do not, accordingly, address the rejection set forth by the Examiner. *Compare* Appeal Br. 11–12 *with* Ans. 6.

Appellants' arguments are wholly unpersuasive of reversible error because they fail to address the rejection as set forth by the Examiner. Further, the arguments are also unpersuasive of error because—as highlighted by the Examiner (Ans. 11–12)—the arguments attack the references individually rather than the combination. When a claim is rejected as obvious over a combination of references, the question is not what the references teach individually, but whether the differences between the claimed invention and the prior art would have been obvious over the combined teachings of the references and what these teachings would have suggested to a person of ordinary skill in the art. *In re Mouttet*, 686 F.3d

1322, 1332–33 (Fed. Cir. 2012); *In re Keller*, 642 F.2d 413, 425 (CCPA 1981).

Rejection III

In rejecting claim 8, the Examiner relies on Xiao and Zhao as set forth in Rejection II (Ans. 6) but, conceding Zhao's method of background correction may not be asymmetric, finds "asymmetric estimation, non-constant level of background is well known in the art" and relies on Mazet for its relevant teaching of "asymmetric estimation, non-constant levels of background" (Ans. 7 (citing Mazet 126, Figs. 2a, 2b)). The Examiner further relies on Mazet for its teaching that "when there are only positive peaks in the spectrum, asymmetric estimation of background gives [the] best result" and concludes one of ordinary skill in the art at the time of the invention would have found it obvious "to use asymmetric estimation of background for mass spectrum, because mass spectrum only has positive peaks." Ans. 7.

Appellants contend that the combination relied on by the Examiner does not teach or suggest all elements of claim 8. Appeal Br. 12–13. Appellants argue that the background estimation method according to the claim is asymmetric in contrast to that of Zhao's symmetric method. Appeal Br. 12. Appellants argue that Mazet differs from that according to the claim because it does not disclose performing an asymmetric estimate of background in a moving window, but rather treats the spectrum as a whole, and does not consider mass spectra. Appeal Br. 13. Appellants further contend that they "considered the references in combination." Reply Br. 6.

Appellants' argument is not persuasive of reversible error because it fails to address the combination as set forth by the Examiner. The

arguments are grounded on deficiencies in the individual references or on modification of Xiao and Zhao to include features from Mazet not relied on by the Examiner in the rejection. Arguments against references individually can not overcome rejections grounded on combinations of references. *Mouttet*, 686 F.3d at 1332–33; *Keller*, 642 F.2d at 425. Arguments as to the additional features from Mazet contrary to what is set forth in the claim are likewise without merit. *Cf. In re Sneed*, 710 F.2d 1544, 1550 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); *In re Nievelt*, 482 F.2d 965, 968 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures."). Thus in neither case are the arguments persuasive of error.

Rejection IV

The Examiner relies on Lynch for its teachings relating to non-small cell lung cancer patients and a drug targeting that cancer that comprises an epidermal growth factor receptor inhibitor. Final Act. 6–7; Ans. 7, 12–13. The Examiner further determines, however, that the recitations as to "a multitude of non-small cell lung cancer patients administered a cancer targeting drug" (claim 3) and as to "the cancer targeting drug compris[ing] an epidermal growth factor receptor inhibitor" (claim 9) merely describe intended uses of the storage device and thus do not further limit the structure. Final Act. 6–7; Ans. 8–9.

Appellants proffer various arguments directed to Lynch and the Examiner's reasoning related to its teachings. Appeal Br. 13–15; Reply Br. 6–9.

We need not reach the proffered arguments. Appellants fail to address the Examiner's findings and conclusions grounded on claims 3 and 9 describing intended uses rather than structural limitations. Appeal Br. 13–15; 6–9. Appellants fail to apprise us, accordingly, of any error in the Examiner's determination that there is no difference in the structure required for Xiao's apparatus to perform the intended function of the claimed apparatus according to claims 3 and 9. Finding the Examiner's determination well-founded that Xiao's device is capable of performing the recited use, for the reasons set forth above in respect to Rejection I, we sustain the Examiner's rejection of claims 3 and 9 on this ground.

DECISION

The Examiner's decision rejecting claims 1, 2–4, 5, 7, and 8–11 is AFFIRMED.

The Examiner's decision rejecting claim 6 is REVERSED.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED-IN-PART